CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-060

MICROBIOLOGY REVIEW

Product Quality Microbiology ReviewReview for HFD 170

10-December-2004

NDA:

21-060-AZ

Drug Product Name

Proprietary:

Prialt®

Non-proprietary:

Ziconotide

Drug Product Classification:

New Molecular Entity/Priority

Review

Review Number:

6

Subject of this Review

Submission Date:

June 25, 2004

Receipt Date:

June 28, 2004

Consult Date:

November 10, 2004

Date Assigned for Review:

November 10, 2004

Submission History (for amendments only)

Previous Submission Dates	Previous Micro. Review Dates	Micro. Reviewer	
October 29, 1999	January 21, 2000	P. Stinavage	
March 22, 2000	May 1, 2000	P. Stinavage	
September 20, 2000	November 30, 2000	P. Stinavage	
December 28, 2000	February 13, 2001	P. Stinavage	
January 26, 2001	May 22, 2001	P. Stinavage	

Applicant/Sponsor

Name:

Elan Pharmaceuticals

Address:

800 Gateway Blvd.

South San Francisco, CA 94080

Representative:

Not provided

Telephone:

Not provided

Name of Reviewer:

Stephen E. Langille, Ph.D.

Conclusion:

Recommended for approval

Appears This Way

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Not applicable

2. SUPPLEMENT PROVIDES FOR: Not applicable

3. MANUFACTURING SITE:



injection in 1, 2, 5, and 20 mL vials

- Intrathecal injection
- 100 ug/mL or 25 ug/mL
- 5. METHOD(S) OF STERILIZATION: Aseptic fill
- 6. PHARMACOLOGICAL CATEGORY: Analgesic
- B. SUPPORTING/RELATED DOCUMENTS: 5 product quality microbiology reviews by P. Stinavage (in DFS).
- C. **REMARKS:** The applicant has provided the following information:
 - A response to the July 25, 2001 approvable letter
 - Information concerning a new 25 ug/mL product formulation
 - Changes and updates for the current 100 ug/mL formulation
 - Information regarding endotoxin limits and dosing information (NDA 21-060-N000-BI, Submitted on December 6, 2004)
 - The applicant provided a response to the product quality microbiology reviewer questions provided on November 30, 2004 (NDA 21-060-N000-BI, Submitted on December 2, 2004).

filename: C:/Reviews/N021060R6.DOC

Executive Summary

I. Recommendations

- A. Recommendation on Approvability NDA 21-060 is recommended for approval from the standpoint of
 product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology
The drug product will be aseptically filled in glass vials and closed

- B. Brief Description of Microbiology Deficiencies No deficiencies were identified based upon the information
 provided
- C. Assessment of Risk Due to Microbiology Deficiencies Not applicable

III. Administrative

- A. Reviewer's Signature
- B. Endorsement Block
 Stephen E. Langille, Ph.D.
 Supervisor/Team Leader
- C. CC Block In DFS

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§ 552(b)(5) Deliberative Process

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/s/

Stephen Langille 12/13/04 07:44:20 AM MICROBIOLOGIST

David Hussong 12/13/04 10:09:10 AM MICROBIOLOGIST

REVIEW FOR HFD-170 OFFICE OF NEW DRUG CHEMISTRY MICROBIOLOGY STAFF MICROBIOLOGIST'S REVIEW #4 OF NDA 21-060 22 May 2001

- A. 1. NDA 21-060 AZ
 APPLICANT: Elan Pharmaceuticals
 800 Gateway Blvd.
 South San Francisco, CA 94080
 - 2. PRODUCT NAME: SNX-11 (ziconotide)

. . .

- 4. METHODS OF STERILIZATION: The drug product is aseptically filled.
- PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
 INDICATION:
 The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.
- B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999
 - 2. DATE OF AMENDMENT: 26 January 2001 (Subject of this Review)
 - 3. RELATED DOCUMENTS: DMF's
 - 4. ASSIGNED FOR REVIEW: 16 May 2001
- C. REMARKS: The product is to be manufactured at either of two sites:

This submission provides the final report of the second ziconotide drug product growth promotion study. The data contained in this submission do not differ substantively from the data submitted in the interim report(NDA 21-060 BC submitted 28 December 2000)(See Microbiologist's Review dated 13 February 2001). For example, results indicate that maintained viability and appeared to flourish throughout the 61-day test period in both the saline control and the product solution.

'also maintained viability throughout the 61-day period in both saline and the product. Counts of all other test organisms dropped below detection limits of the assay by Day 3 of the test. These results are essentially the same as those obtained at the 31-day time point. The conclusions remain the same as in the 13 February 2001 review.

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D. CONCLUSIONS: The data presented indicate that at least two of the test organisms replicate over the 61-day test period. In addition, maintained viability over the test period. However, if the health professionals refilling the pump reservoir maintain strict aseptic technique during the procedure the risk of contaminating the reservoir should not exceed the rate of contamination observed with other hospital performed aseptic procedures. The clinical reviewer should assess if the therapeutic advantages of use of this product in the implanted infusion pump outweigh the

Elan Pharmaceuticals, NDA 21-060, Ziconotide, Microbiologist's Rev. #4

risk of infection caused by contamination of and subsequent bacterial multiplication in the pump reservoir.

The manufacturing process for the drug product remains approvable on the basis of sterility assurance. Specific comments regarding the manufacturing process provided in the Microbiologist's Review dated 18 April 2000 remain to be resolved.

Paul Stinavage, Ph.D.

cc:

Original NDA 21-060 HFD-805/Stinavage/Consult File HFD-170/Div File/L. Governale/McCormick/Hertz/Koble

Drafted by: P. Stinavage, 22 May 2001 R/D initialed by P. Cooney

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Paul Stinavage 2/13/01 02:10:04 PM MICROBIOLOGIST Interim results of second growth promotion study.

Peter Cooney 2/13/01 03:35:00 PM MICROBIOLOGIST



REVIEW FOR HFD-170 OFFICE OF NEW DRUG CHEMISTRY MICROBIOLOGY STAFF MICROBIOLOGIST'S REVIEW #3 OF NDA 21-060 13 February 2001

- A. 1. NDA 21-060 BC
 APPLICANT: Elan Pharmaceuticals
 800 Gateway Blvd.
 South San Francisco, CA 94080
 - 2. PRODUCT NAME: SNX-11 (ziconotide)
 - 3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is intended for intrathecal administration. The product strength is 100 µg/mL in 2, 5, mL vials.
 - 4. METHODS OF STERILIZATION: The drug product is aseptically filled.
 - PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
 INDICATION:
 The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.
- B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999
 - 2. DATE OF AMENDMENT: 28 December 2000 (Subject of this Review)
 - 3. RELATED DOCUMENTS: DMF's
 - 4. ASSIGNED FOR REVIEW: 18 January 2001
- C. REMARKS: The product is to be manufactured at either of two sites:

Elan Pharmaceuticals, NDA 21-060, Ziconotide, Microbiologist's Rev. #3

This submission provides the interim report of the second ziconotide drug product growth promotion study.

D. CONCLUSIONS:

The clinical reviewer should assess if the therapeutic advantages of use of this product in the implanted infusion pump outweigh the risk of infection caused by contamination of and subsequent bacterial multiplication in the pump reservoir.

The manufacturing process for the drug product remains approvable on the basis of sterility assurance. Specific comments regarding the manufacturing process provided in the Microbiologist's Review dated 18 April 2000 remain to be resolved.

Paul Stinavage, Ph.D.

cc: Original NDA 21-060
HFD-805/Stinavage/Consult File
HFD-170/Div File/L. Governale/McCormick/Hertz/Koble

Drafted by: P. Stinavage, 13 February 2001 R/D initialed by P. Cooney

- § 552(b)(4) Trade Secret / Confidential
- § 552(b)(5) Deliberative Process
- _____ § 552(b)(5) Draft Labeling

Paul Stinavage 11/30/00 06:09:27 AM MICROBIOLOGIST Final report of initial drug product growth promotion study.

Peter Cooney 11/30/00 11:15:35 AM MICROBIOLOGIST

REVIEW FOR HFD-170 OFFICE OF NEW DRUG CHEMISTRY MICROBIOLOGY STAFF MICROBIOLOGIST'S REVIEW #2 OF NDA 21-060 14 November 2000

A. 1. NDA 21-060 BI

APPLICANT:

Elan Pharmaceuticals

800 Gateway Blvd.

South San Francisco, CA 94080

2. PRODUCT NAME: SNX-11 (ziconotide)

- 3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is intended for intrathecal administration. The product strength is 100 µg/mL in 2, 5, . `mL vials.
- 4. METHODS OF STERILIZATION: The drug product is aseptically filled.
- PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
 The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.
- B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999
 - 2. DATE OF AMENDMENT: 20 September 2000 (Subject of this Review)
 - 3. RELATED DOCUMENTS: DMF's
 - 4. ASSIGNED FOR REVIEW: 25 September 2000
- C. REMARKS: The product is to be manufactured at either of two sites:

This submission provides the final report of the first ziconotide drug product growth promotion study.

D. CONCLUSIONS: Review of this submission does not alter the "Not Approvable" conclusion in the review dated 18 April 2000.

Paul Stinavage, Ph.D.

cc: Original NDA 21-060
HFD-805/Stinavage/Consult File
HFD-170/Div File/L. Governale/McCormick/Chamberlin

Drafted by: P. Stinavage, 14 September 2000 R/D initialed by P. Cooney

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REVIEW FOR HFD-170 OFFICE OF NEW DRUG CHEMISTRY MICROBIOLOGY STAFF MICROBIOLOGIST'S REVIEW #2 OF NDA 21-060 18 April 2000

A. 1. NDA 21-060 BI '

APPLICANT:

Elan Pharmaceuticals 800 Gateway Blvd.

South San Francisco, CA 94080

- 2. PRODUCT NAME: SNX-11 (ziconotide)
- 3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is intended for intrathecal administration. The product strength is 100 μg/mL in 2, 5, mL vials.
- 4. METHODS OF STERILIZATION: The drug product is aseptically filled.
- 5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
 The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.
- B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999
 - 2. DATE OF AMENDMENT: 22 March 2000 (Subject of this Review)
 - 3. RELATED DOCUMENTS: DMF's
 - 4. ASSIGNED FOR REVIEW: 28 March 2000
- C. REMARKS: The product is to be manufactured at either of two sites:

The manufacturing process used at ____ differs from that used at - Following vial filling at At — the filled vials

D. CONCLUSIONS: The application is not recommended for approval on the basis of microbiological safety. Specific comments are provided in "E. Review Notes" and "List of Microbiology Deficiencies and Comments". Moreover, the concerns communicated (see Teleconference with applicant minutes dated 30 March 2000, Letter to Applicant drafted 7 April 2000 by L. Governale) to the applicant regarding the use of an implantable pump for delivery of this drug product remain to be resolved.

Paul Stinavage, Ph.D.

H 18/07

Original NDA 21-060 CC:

HFD-805/Stinavage/Consult File

HFD-170/Div File/L. Governale/McCormick/D'Sa/Chamberlin/

Theodorakis

Elan Pharmaceuticals, NDA 21-060, Ziconotide, Microbiologist's Rev. #2 of pre-NDA

Drafted by: P. Stinavage, 18 April 2000 R/D initialed by P. Cooney

- _____ § 552(b)(4) Trade Secret / Confidential
- § 552(b)(5) Deliberative Process
- _____ § 552(b)(5) Draft Labeling

JAN 20 2000

REVIEW FOR HFD-170 OFFICE OF NEW DRUG CHEMISTRY MICROBIOLOGY STAFF MICROBIOLOGIST'S REVIEW #1 OF Pre-NDA 21-060 13 January 2000

A. 1. NDA 21-060

APPLICANT:

Elan Pharmaceuticals

800 Gateway Blvd.

South San Francisco, CA 94080

2. PRODUCT NAME: SNX-11 (ziconotide)

- 3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is intended for intrathecal administration. The product strength is 100 µg/mL in 2, 5, mL vials.
- 4. METHODS OF STERILIZATION: The drug product is aseptically filled.
- 5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:

 The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.
- B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999
 - 2. DATE OF AMENDMENT: (none)
 - 3. RELATED DOCUMENTS: DMF's
 - 4. ASSIGNED FOR REVIEW: 10 November 1999
- C. REMARKS: The application is a pre-NDA CMC submission that includes microbiology information. The product is to be manufactured at either of two sites:

The manufacturing process used at _____ differs from that used at ____ Following vial filling at _____ At __` the filled vials are loaded into a

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns. Specific comments are provided in "E. Review Notes" and "List of Microbiology Deficiencies and Comments".

Paul Stinavage, Ph.D.

cc: Original NDA 21-060
HFD-805/Stinavage/Consult File
HFD-170/Div File/McCormick/D'Sa/Chamberlin/
Theodorakis

Drafted by: P. Stinavage, 13 January 2000 R/D initialed by P. Cooney

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§ 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH AND HUM 'N

PEOLIECT FOR CONSULTATION

SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
Pivision/Office): HFD-160/ Microbiology				FROM: HFD-170/Dr. Cynthia McCarmick	
Бжт ё 11-2-99	IND NO.		NDA # 21-060	TYPE OF DOCUMENT	DATE OF DOCUMENT 10-29-99
NAME OF DRUG Ziconotide Soln. Injectable PRIORITY HIGH Prio		CONSIDERATION ity	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 1-25-2000	
NAME OF FIRM: Elan I	Pharmaceutic	cals			
			REASION I	FOR REQUEST	
			I. GE	ENERAL	
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY PRENDA MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMEN			ND OF PHASE II MEETI ESUBMISSION AFETY/EFFICACY APER NDA	LABELING REVISION *ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW	
			II. BIO	METRICS	
STATISTICAL EVALUATION BRANCH				STATISTICAL APPLICATION BRANCH	
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW R (SPECIFY BELOW):				CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):	
			III. BIOPHA	RMACEUTICS	
DISSOLUTION BIOAVAILABILTY STUD PHASE IV STUDIES	DIES			DEFICIENCY LETTER RESPON PROTOCOL-BIOPHARMACEUT IN-VIVO WAIVER REQUEST	
			IV. DRUG	EXPERIENCE	
PHASE IV SURVEILLANDRUGUSE & POPULA				REVIEW OF MARKETING EXPI	ERIENCE, DRUG USE AND SAFETY

DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

SUMMARY OF ADVERSE EXPERIENCE

POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The firm has submitted a pre-NDA CMC submission which includes microbiology section. The chemistry reviewer is M. Theodorakis, phone 827-7425. This application is a priority for our Division, and we are asking that you provide us a response by January 25, 2000.

Please review the attached correspondence (2 volumes). Any questions please contact, Dr. Abi D'Sa Chemistry Team Leader or Nancy Chamberlin, CSO at 7-7410. Thank you for your assistance.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

□ MAIL

N HAND

SIGMATURE OF RECEIVER

SIGNATURE OF DELIVERER



ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21060/000

: 1P

Sponsor: ELAN PHARMS

Org Code

: 170

7475 LUSK BLVD

Priority

SAN DIEGO, CA 92121

Stamp Date : 28-DEC-1999

Brand Name :

ZICONOTIDE SOLUTION 100MCG/ML

PDUFA Date : 28-DEC-2004

1/2/5 - ML

Action Goal :

Estab. Name:

District Goal: 29-OCT-2004

Generic Name:

ZICONOTIDE SOLUTION 100MCG/ML

1/2/5 🗪 ML

Dosage Form:

(INJECTION)

Strength :

0.1 MG/ML

FDA Contacts: S. STRADLEY

Project Manager (HFD-170)

301-827-7430

M. THEODORAKIS

Review Chemist (HFD-170)

301-827-7425

R. HARAPANHALLI

Team Leader

(HFD-170)

301-827-7410

Overall Recommendation:

ACCEPTABLE on 23-DEC-2004by S. ADAMS (HFD-322) 301-827-9051

ACCEPTABLE on 02-APR-2001by J. D AMBROGIO(HFD-322) 301-827-

9049

ACCEPTABLE on 12-FEB-2001by S. FERGUSON (HFD-322) 301-827-

9009

on 21-JUN-2000by S. FERGUSON (HFD-322) 301-827-WITHHOLD

9009

Establishment : CFN :

FEI :

DMF No:

AADA:

Responsibilities:

Profile :

CTL

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

13-DEC-04

Decision :

ACCEPTABLE

Reason

DISTRICT RECOMMENDATION

Establishment :

DMF No:

AADA:

Responsibilities:

Profile : CTL

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-NOV-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment :

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No:

AADA:

Responsibilities:

Profile : CTL

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-OCT-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment :

ELAN BIOPHARMACEUTICALS

800 GATEWAY BLVD

SOUTH SAN FRANCISCO, CA 94080

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

21-DEC-04

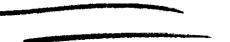
Decision :

Reason

ACCEPTABLE

DISTRICT RECOMMENDATION

Establishment :



DMF No:

AADA:

Responsibilities:

Profile : CTL

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

23-DEC-04

Decision :

ACCEPTABLE

Reason

DISTRICT RECOMMENDATION

Establishment :

DMF No:

AADA:

Responsibilities:

I

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile :

SVS

OAI Status: NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

29-OCT-04

Decision :

ACCEPTABLE

Reason

DISTRICT RECOMMENDATION

Establishment :

DMF No:

AADA:

Responsibilities:

Profile :

CTL

OAI Status: NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

25-OCT-04

Decision :

ACCEPTABLE

Reason

BASED ON PROFILE

Establishment :

DMF No:

AADA:

Responsibilities:

Profile :

CTL

OAI Status:

NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

09-DEC-04

Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		
Establishment :			· · · · · · · · · · · · · · · · · · ·
	-		
DMF No:		AADA:	
Responsibilities:			
Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-OCT-04		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

AADA:

Establishment :

DMF No:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities:

Profile :

CSN

OAI Status: NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

29-OCT-04

Decision :

ACCEPTABLE

Reason :

DISTRICT RECOMMENDATION